EXHIBIT 1

Combination Therapy With Etanercept and Anakinra in the Treatment of Patients With Rheumatoid Arthritis Who Have Been Treated Unsuccessfully With Methotrexate

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Objective. To determine the potential for additive or synergistic effects of combination therapy with the selective anti–tumor necrosis factor α agent etanercept and the anti–interleukin-1 agent anakinra.

Methods. Two hundred forty-four patients in whom rheumatoid arthritis (RA) was active despite methotrexate therapy were treated with subcutaneous etanercept only (25 mg twice weekly), full-dosage etanercept (25 mg twice weekly) plus anakinra (100 mg/day), or half-dosage etanercept (25 mg once weekly) plus anakinra (100 mg/day) for 6 months in a double-blind study at 41 centers in the US. Patients had never previously received anticytokine therapy. Patient response was measured with the American College of Rheumatology (ACR) core set criteria, a health-related quality-of-life questionnaire, and the Disease Activity Score. Safety was assessed by the number of adverse events and clinical laboratory values. Plasma concentrations of both agents and antibody formation against both agents were also assessed.

Results. Combination therapy with etanercept plus anakinra provided no treatment benefit over etanercept alone, regardless of the regimen, but was associated with an increased safety risk. Thirty-one percent of the patients treated with full-dosage etanercept plus anakinra achieved an ACR 50% response, compared with 41% of the patients treated with etanercept only. This result was not statistically significant ($P = 0.914$). The incidence of serious infections (0% for etanercept alone, 3.7–7.4% for combination therapy), injection-site reactions, and neutropenia was increased with combination therapy. Combination therapy had no effect on the pharmacokinetics or immunogenicity of either agent.

Conclusion. Combination therapy with etanercept and anakinra provides no added benefit and an increased risk compared with etanercept alone and is not recommended for the treatment of patients with RA.

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by inflammation that often leads to the progressive destruction of articular structures and significant disability. The etiology of RA remains unclear, but it is thought to be mediated in part by antigen-driven T cells and macrophages that produce interleukin-1 (IL-1) and tumor necrosis factor α (TNFα), 2 cytokines involved in the inflammatory cascade (1–3). Specific blockade of these individual cytokines has recently been shown in large, place-controlled trials to be safe and effective in the treatment of RA (4–9).

Although selective anticytokine therapy has improved patient outcomes, it does not necessarily produce disease remission. Thus, the more aggressive treatment option of combining anticytokine agents has been explored in animal studies. Combination treatment with anakinra, a recombinant IL-1 receptor antagonist (IL-1Ra) (Kineret; Amgen, Thousand Oaks, CA), and polyethylene glycol–conjugated soluble TNF receptor type I

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sulted in synergistic improvement in the symptoms of juvant-induced and collagen-induced arthritis in rats lative to the improvement observed with either agent one (10,11). Additive or synergistic improvement was en with a variety of dose combinations of each agent, it synergistic improvement was particularly evident nen suboptimal doses of each agent were given in ombination.

The present study was designed to test the hypothe-s that combination therapy with the anti-TNF agent anercept, a soluble TNFα receptor (Enbrel; Amgen), nd the anti-IL-1 agent anakinra at their approved osages would safely provide superior efficacy relative to tanercept alone in patients with RA. Secondarily, the udy examined the possibility that anakinra given with tanercept at a dosage of 25 mg once weekly (half the pproved weekly dose) would still provide superior fficacy compared with full-dosage etanercept alone.

PATIENTS AND METHODS

Patients. This study enrolled patients who were at least 8 years old and had a >6-month history of RA, as diagnosed by the American College of Rheumatology (ACR) classifica-ion criteria (12). Patients had at least 6 swollen joints and 9 ender/painful joints and at least 2 of the following: morning tiffness lasting at least 45 minutes, a serum C-reactive protein CRP) level of at least 1.5 mg/dl, or an erythrocyte sedimen-ation rate (ESR) of at least 28 mm/hour. Patients had received methotrexate (MTX) for at least 16 weeks, with the dosage stable at 10–25 mg/week for at least 8 weeks. All patients gave informed consent, and the study protocol was approved by the institutional review boards for each study site.

Patients were not eligible to enroll in the study if they had received any disease-modifying antirheumatic drug other than MTX within the past 4 weeks, had ever been treated with anakinra or any protein-based TNFα inhibitor (e.g., etaner-cept, infliximab), had received any intraarticular or systemic corticosteroid injections within the past 4 weeks, or had a recent history of significant infection or other important concurrent illness.

Study design and treatment. Patients were randomly assigned in a 1:1:1 ratio to receive 25 mg of etanercept twice weekly plus anakinra placebo once daily, 25 mg of etanercept once weekly plus 100 mg of anakinra daily, or 25 mg of etanercept twice weekly plus 100 mg of anakinra once daily (hereafter referred to a etanercept only, half-dosage etaner-cept plus anakinra, and full-dosage etanercept plus anakinra, respectively). Both etanercept and anakinra were administered subcutaneously for 24 weeks. In order to blind patients to the treatment assignment, additional sham injections of etanercept were administered as necessary, so that all patients received twice weekly injections of etanercept/sham and once daily injections of anakinra or matched placebo. Patients continued to receive stable doses of MTX and other medications (e.g., corticosteroids) throughout the study. After screening, patients were evaluated at baseline (day 1) and at weeks 2, 4, 8, 12, 16,

20, and 24, with followup evaluation 4 weeks after completion or at the time of early discontinuation.

Endogenous human IL-1Ra was isolated, purified, and produced by recombinant DNA technology using *Escherichia coli* fermentation. The resulting product, anakinra, is identical to the naturally occurring nonglycosylated form of human IL-1Ra except for the addition of an N-terminal methionine residue. Anakinra was provided by Amgen in single-use vials as a liquid containing 1 ml of 100 mg/ml anakinra. The formula-tion consisted of sodium citrate, sodium chloride, disodium EDTA, and polysorbate 80. The placebo formulation was the same, but without anakinra. Both solutions were pH 6.5.

Etanercept is a soluble TNF receptor fusion protein produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system. Etanercept was supplied by Amgen in 25-mg single-use vials containing etanercept lyophilized powder, mannitol, sucrose, and tromethamine. After reconstitution with bacteriostatic water, the solution had a mean ($\pm$SD) pH of 7.4 $\pm$ 0.3.

Efficacy assessment. At every study visit, patients were assessed for the components of the ACR core set of disease activity measures (13), the modified Disease Activity Score (DAS) (14), the European League Against Rheumatism (EU-LAR) response (14), and the duration of morning stiffness. A health-related quality-of-life evaluation with the Short Form 36 (SF-36) healthy survey (15) was performed at baseline and at weeks 4, 12, and 24 (or at the time of early termination).

The primary end point was the proportion of patients achieving an ACR 50% (ACR50) response (16) at week 24. Secondary efficacy end points included the ACR20 and ACR70 response rates at week 24, the ACR response at week 12, the sustained ACR20 response (response for at least 4 monthly measurements, not necessarily consecutive, with 1 occurring at month 6), a good or moderate EULAR response at week 24, improvement in the ACR core criteria compo-nents, duration of morning stiffness, the DAS, and the SF-36 score.

Patients were considered ACR50 responders if they had at least a 50% reduction in the number of tender and swollen joints and in 3 of the following 5 measures: patient's assessment of disease activity by visual analog scale (VAS), physician's assessment of disease activity by VAS, patient's assessment of pain by VAS, the disability score as measured by the Health Assessment Questionnaire (17), and acute-phase reactants (CRP or ESR). The joint counts (66 joints evaluated for swelling, and 68 joints evaluated for tenderness/pain) were assessed by the same qualified independent assessors at each study center throughout the study. To preserve blinding of the study, injection sites were covered with clothing during the joint counts to insure that the assessors would not be influ-enced by injection-site reactions.

Safety and pharmacokinetic assessment. Safety assess-ment data that were collected at every study visit were the number of adverse events/infectious events and the clinical laboratory values. An adverse event was defined as follows: "Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relation-ship with this treatment" (18). A serious adverse event was defined as follows: "Any untoward medical occurrence that at

Table 1. Baseline characteristics of study patients*

Characteristic	Etanercept only (n = 80)	Half-dosage etanercept + anakinra (n = 81)	Full-dosage etanercept + anakinra (n = 81)
% female	82.5	71.6	77.8
% white race	86.3	77.8	75.3
Age, years	54.4 ± 13.6	53.8 ± 11.8	55.7 ± 13.0
% age ≥ 65 years	25.0	18.5	29.6
Weight, kg	75 ± 18	82 ± 21	80 ± 23
Duration of RA, years	9.7 ± 9.4	9.5 ± 10.3	10.6 ± 9.8
% rheumatoid factor positive	65.0	75.3	71.6
% receiving corticosteroids	48.8	54.3	44.4
NSAID use, %	96.3	95.1	96.3
MTX dosage, mg/week	16.1 ± 4.5	16.2 ± 4.2	15.7 ± 5.0
No. of tender/painful joints	31.0 ± 14.2	31.0 ± 15.4	35.9 ± 14.9
No. of swollen joints	21.4 ± 9.4	19.8 ± 9.6	23.4 ± 12.0
HAQ score	1.5 ± 0.6	1.5 ± 0.6	1.6 ± 0.6
Serum CRP, mg/dl	2.0 ± 2.2	2.4 ± 3.5	2.0 ± 2.5
ESR, mm/hour	44.6 ± 21.51	49.2 ± 22.81	49.9 ± 23.94
Duration of morning stiffness, minutes	145.3 ± 102.3	154.4 ± 162.1	159.5 ± 134.0
SF-36 score			
Physical component	28.7 ± 9.7	28.8 ± 7.9	29.1 ± 7.9
Mental component	46.9 ± 12.3	47.9 ± 10.9	44.5 ± 11.9

* Except where indicated otherwise, values are the mean ± SD. Etanercept only = etanercept 25 mg twice weekly; half-dosage etanercept + anakinra = etanercept 25 mg once weekly plus anakinra 100 mg daily; full-dosage etanercept + anakinra = etanercept 25 mg twice weekly plus anakinra 100 mg daily; RA = rheumatoid arthritis; NSAID = nonsteroidal antiinflammatory drug; MTX = methotrexate; HAQ = Health Assessment Questionnaire; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; SF-36 = Short Form 36.

any dose results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect" (18).

Blood samples were collected for measurement of plasma anakinra and etanercept concentrations (at baseline and weeks 4, 12, and 24 [or at the time of early termination]) and anti-anakinra and anti-etanercept antibodies (at baseline and weeks 12 and 24 [or at the time of early termination]). Plasma anakinra concentrations were assessed by antibody-capture enzyme-linked immunoassay (ELISA), and plasma etanercept concentrations were assessed by a solid-phase sandwich ELISA kit. Antibody samples testing positive in a screening biosensor immunoassay (Biacore, Uppsala, Sweden) were retested for neutralizing antibodies, using a bioassay.

Statistical analysis. Results were analyzed using a modified intent-to-treat method that included all randomized patients who received at least 1 dose each of anakinra/placebo and etanercept/sham. Patients with missing ACR scores at a particular visit were considered nonresponders at that visit.

The primary comparison was the full-dosage etanercept plus anakinra group against the etanercept-only group. The analysis was 1-tailed for the primary comparison and 2-tailed for the secondary comparisons. Odds ratios (ORs) and their confidence intervals (CIs) were calculated for comparisons between groups. Binary efficacy end points were analyzed using a logistic regression model. Continuous end points were analyzed over time using a repeated-measures mixed model.

Adverse events were tabulated for comparison across treatment groups, and summary statistics were calculated for laboratory values.

RESULTS

Characteristics of the study patients. The baseline demographics and disease characteristics of the patients are shown in Table 1. Most of the patients were women with long-standing and very active disease. Characteristics were balanced across treatment groups. Com-
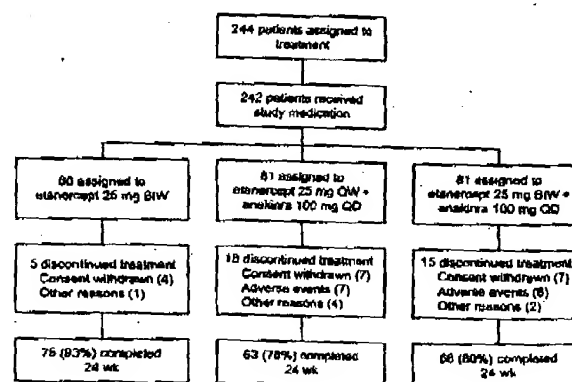
Figure 1. Disposition of patients. Other reasons for premature withdrawal included protocol violations and patients being lost to followup. BIW = twice weekly; QW = once weekly; QD = once daily.
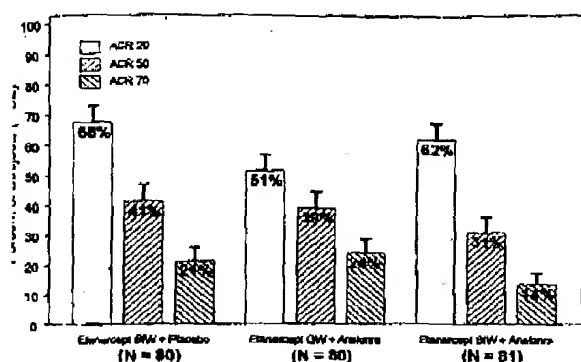
Figure 2. Percent of patients achieving an American College of Rheumatology 20% (ACR20), ACR50, or ACR70 response at week 4. BIW = twice weekly; QW = once weekly.

ɪletion rates ranged from 78% to 93%, with the highest ɪate in the etanercept-only group (Figure 1). Signifiɪantly fewer patients in this group withdrew as a result of ɪdverse events compared with the combination-therapy ɪroups.

Efficacy results. Patients in all treatment groups ɪhowed improvement from baseline at week 24 (Figure ɪ). Therapy in the etanercept-only group resulted in an ACR50 of 41%, compared with 31% in the full-dosage ɪtanercept plus anakinra group ($P = 0.914$, by 1-tailed ɪ-test). The OR for achieving an ACR50 response in the ɪull-dosage etanercept plus anakinra group relative to ɪhat in the etanercept-only group was 0.64 (90% CI ɪ.37–1.09). The OR for achieving an ACR50 response in ɪhe etanercept-only group relative to that in the half-

dosage etanercept plus anakinra group was 1.11 (95% CI 0.59–2.09). For the comparison of patients in the full-dosage (twice weekly) combination-therapy group relative to those in the low-dosage (once weekly) combination therapy group, the OR was 0.71 (95% CI 0.37–1.35).

Because the dropout rate was higher in the groups receiving combination therapy, it was important to determine whether this influenced the efficacy results. Sensitivity analyses, including a completers analysis (all patients who completed the study) and a last observation carried forward analysis, yielded results similar to those observed in the modified intent-to-treat analysis (data not shown), indicating that differential dropout rates did not influence the outcome. In addition, results were unaffected when they were adjusted for baseline covariates (data not shown).

Evaluation of the ACR20 and ACR70 response rates confirmed that combination therapy was not superior to etanercept alone. The only comparison yielding a statistically significant difference between treatments indicated that at week 24, the ACR20 response of patients treated with etanercept alone was superior to that of patients treated with etanercept once weekly plus anakinra (OR 1.98, 95% CI 1.05–3.78; $P = 0.037$).

Between 43% and 54% of patients in each treatment group achieved a sustained ACR20 response during the study, and most patients achieved a EULAR response at week 24 (79% of patients in etanercept-only group, 73% of those in the full-dosage etanercept plus anakinra group, and 66% of patients in the half-dosage etanercept plus anakinra group received a good or moderate rating). At week 24, the mean percent reduction from baseline in the DAS was 39% in the
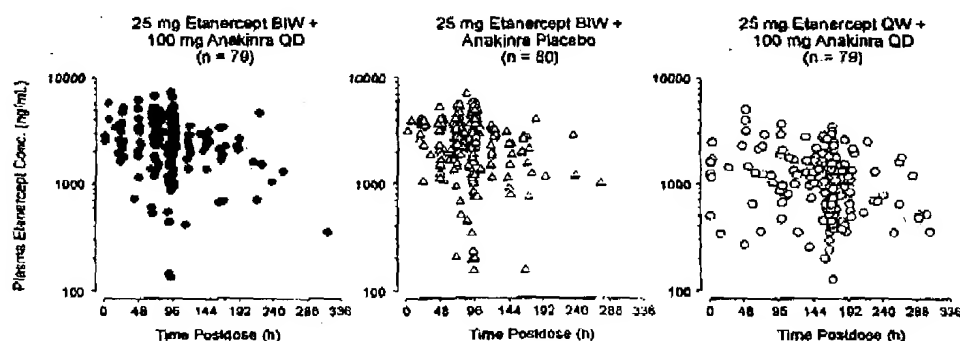

Figure 3. Individual plasma etanercept concentrations (Conc). Because the results at each week indicated that the pharmacokinetic steady state of etanercept was reached by week 4, the data for all visits (weeks 4, 12, and 24) were pooled for analysis. BIW = twice weekly; QW = once weekly; QD = once daily; h = hours.
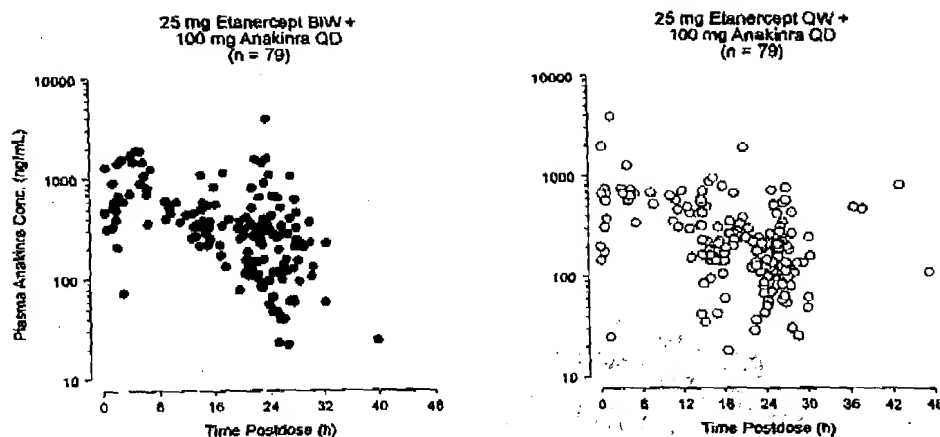
Figure 4. Individual plasma anakinra concentrations. Because the results at each week indicated that the pharmacokinetic steady state of anakinra was reached by week 4, the data for all visits (weeks 4, 12, and 24) were pooled for analysis. See Figure 3 for definitions.

etanercept-only group, 40% in the half-dosage etanercept plus anakinra group, and 41% in the full-dosage etanercept plus anakinra group. Radiographs were not obtained in this study.

Pharmacokinetics. Plasma concentrations for weeks 4, 12, and 24 indicated that the pharmacokinetic steady state was reached by week 4 for both etanercept and anakinra, and thus the data for all visits were pooled for analysis. The pharmacokinetics of each agent appeared unaffected by the concomitant administration of the other (Figures 3 and 4). Plasma concentrations of anakinra and etanercept were similar to those observed

in previous studies of anakinra or etanercept alone (Genovese MC, et al: unpublished observations).

Safety. The proportion of patients reporting adverse events was similar for each treatment group (90–95%) (Table 2). However, combination therapy with anakinra and etanercept was associated with a higher overall incidence of serious adverse events, events causing patient withdrawal from study, and injection-site reactions.

Serious adverse events were generally individual occurrences, with no single category of event accounting for the increase observed with combination therapy

Table 2. Incidence of adverse events during treatment*

Event	Etanercept only (n = 80)	Half-dosage etanercept + anakinra (n = 81)	Full-dosage etanercept + anakinra (n = 81)
Any adverse event	72 (90.0)	77 (95.1)	76 (93.8)
Most common adverse events			
Injection-site reaction	32 (40.0)	55 (67.9)	57 (70.4)
Upper respiratory infection	16 (20.0)	9 (11.1)	11 (13.6)
Any adverse event causing withdrawal	0 (0)	7 (8.6)	6 (7.4)
Any serious adverse event	2 (2.5)	4 (4.9)	12 (14.8)
Any infection	32 (40.0)	30 (37.0)	38 (46.9)
Infection resulting in antibiotic administration or hospitalization	0 (0.0)	3 (3.7)	6 (7.4)
Infection leading to withdrawal	0 (0.0)	2 (2.5)	2 (2.5)
Serious infection	0 (0)	3 (3.7)	6 (7.4)
Serious pneumonia	0 (0)	1 (1.2)	2 (2.5)
Serious cellulitis	0 (0)	1 (1.2)	2 (2.5)

* Values are the number (%) of patients. See Table 1 for definitions.

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Table 3. Serious adverse events that occurred during the study*

Event	Etanercept only (n = 80)	Half-dosage etanercept + anakinra (n = 81)	Full-dosage etanercept + anakinra (n = 81)
Cellulitis	0 (0)	1 (1.2)	2 (2.5)
Pneumonia	0 (0)	1 (1.2)	1 (1.2)
Pneumonia and pulmonary fibrosis leading to respiratory insufficiency	0 (0)	0 (0)	1 (1.2)
Gastroenteritis	0 (0)	0 (0)	1 (1.2)
Herpes zoster	0 (0)	0 (0)	1 (1.2)
Lymphoma, malignant	0 (0)	0 (0)	1 (1.2)
Neuralgia	0 (0)	0 (0)	1 (1.2)
Back pain	0 (0)	0 (0)	1 (1.2)
Chest pain, cardiac	0 (0)	0 (0)	1 (1.2)
Chest pain, noncardiac	0 (0)	0 (0)	1 (1.2)
Pyelonephritis	0 (0)	0 (0)	1 (1.2)
Transient ischemic attack	0 (0)	0 (0)	1 (1.2)
Arrhythmia, atrial	1 (1.3)	0 (0)	0 (0)
Dyspnea	0 (0)	1 (1.2)	0 (0)
Gastric ulcer, hemorrhage	0 (0)	1 (1.2)	0 (0)
Personality disorder	1 (1.3)	0 (0)	0 (0)
Pneumonitis	0 (0)	1 (1.2)	0 (0)

* Values are the number (%) of patients. See Table 1 for definitions

(Table 3). However, infections accounted for serious events in 9 of 16 patients receiving combination therapy. The reported serious infections were as follows: pneumonia and cellulitis (3 patients each), herpes zoster (1 patient), pneumonitis (1 patient), and pyelonephritis (1 patient). One 70-year-old patient with pulmonary fibrosis was diagnosed as having pneumonia and died of pulmonary insufficiency. Serious infections occurred an average of 2 months after exposure to combination treatment (range 1 week to 5 months) in patients whose mean age was 60 years (range 42–77 years). No cases of tuberculosis or opportunistic infections were reported.

The incidence of injection-site reactions was more than 50% higher with combination therapy than with etanercept alone. These reactions were transient, rarely severe (a combined incidence of 2% in the combination-therapy groups), and typically involved no clinical sequelae. However, they were the most common cause of adverse event–related withdrawal during the study for patients receiving combination therapy, accounting for 5 of 13 adverse event–related withdrawals. Injection-site reactions were less likely to occur after the first month of therapy.

The mean neutrophil counts decreased to a similar extent in all 3 groups within the first 2 weeks of initiating treatment but remained stable thereafter. Two patients in the full-dosage etanercept plus anakinra group experienced neutropenia (neutrophil count $<1.0 \times 10^9$/liter) during the study. Both patients completed the study, and no clinical events were associated

with the neutropenia. No subjects had changes in the neutrophil count that appeared to be associated with their serious infectious episodes. None of the subjects who experienced serious infectious episodes experienced neutropenia. No other clinically significant trends in the laboratory results were apparent. Three patients receiving anakinra and no patients receiving etanercept had evidence of potentially neutralizing anti-anakinra and anti-etanercept antibodies, respectively. The presence of antibodies had no apparent effect on efficacy or safety.

DISCUSSION

The clinical hypothesis for this study, that combination treatment with selective anticytokine therapies (etanercept and anakinra) would safely provide superior improvement in the signs and symptoms of RA compared with etanercept alone, proved false. Analyses of the primary efficacy end point, the ACR50 response at week 24, showed no significant differences between groups regardless of the combination regimen used (etanercept twice weekly or once weekly). In fact, patients who received etanercept only in this study had the highest ACR responses, similar to those seen in previous studies of etanercept (4,8), and encountered the fewest safety problems.

Results of preclinical experiments suggested that simultaneous blockade of IL-1 and TNFα would be more effective than either approach alone in inhibiting

progression of RA, with a combination of suboptimal doses of each anticytokine agent providing a synergistic effect. The reasons for the discrepancy between the preclinical and clinical results are unclear, but several theories present themselves. First, there may have been a negative interaction between the compounds. This theory seems unlikely, because the pharmacokinetic results show that plasma concentrations for both agents remained unchanged relative to observations for each agent independently. Also, anakinra is eliminated renally (19–21), while etanercept is eliminated by the Kupffer cells of the liver (Genovese MC, et al: unpublished observations). It is also unlikely that anakinra and etanercept would bind and block the effect of each other.

Second, anti-anakinra antibodies could be responsible for the lack of benefit of combination therapy. This too is unlikely, because a low percentage of patients had potentially neutralizing anti-anakinra antibodies, and the antibody results from this study were consistent with the antibody data from other anakinra studies in which efficacy was demonstrated. Third, anti-TNF therapy could have down-regulated IL-1 expression, rendering any impact of anti–IL-1 therapy negligible. This remains a possibility, although it would not explain the inconsistency between the clinical and preclinical results. Fourth, the degree of overlap and interplay between IL-1 and TNF may leave little room for improvement beyond the efficacy attainable with an effective TNF inhibitor. This is an intriguing possibility that requires further study.

The safety results for this study showed that combination anticytokine therapy was associated with a higher incidence of serious infections than was observed with the use of etanercept alone. These results are comparable with what was previously reported in a small open-label study of the combination of etanercept and anakinra (22). Many patients in this study were receiving a combination of 4 potentially immunosuppressive agents, including corticosteroids, MTX, anakinra, and etanercept, all of which could have contributed to this finding. Combination therapy was also more commonly associated with neutropenia, which is probably not surprising because decreases in the neutrophil count have been associated with both etanercept and anakinra (Genovese MC, et al: unpublished observations). It is notable, however, that in this study neutropenia was not associated with the risk of serious infection.

These results suggest that use of combination treatment with anakinra and etanercept is not justified in patients with RA who are naive to biologic therapy.

However, the possibility that combination anticytokine treatment could benefit certain patients cannot be excluded based on this relatively small study. The response to combination therapy might be different in patients with partial or inadequate responses to prior anticytokine treatment, for example, although the safety concerns raised by this study would remain. Furthermore, these results do not preclude the possibility of successful combination therapy with future agents selectively blocking other pathways.

Overall, the results from this study provide no evidence of an additional treatment benefit of combination therapy with etanercept plus anakinra in patients with active RA despite the use of MTX. In fact, the combination posed an increased risk of serious infection and neutropenia. Treatment with etanercept or anakinra alone, or either agent in combination with MTX, has been demonstrated to be effective and safe in previous studies, and the findings from this study do not affect the profiles of the individual compounds. The findings do raise important questions about the role of each of these cytokines in the pathophysiology of RA and other inflammatory diseases. The development of anticytokine therapies has epitomized the translation of research from bench to bedside, and the results of this study highlight the need to translate these results back to the bench to better understand the interrelationship of these cytokines in human disease and to explain the incongruity of the preclinical and clinical findings.

ACKNOWLEDGMENTS

APPENDIX A: MEMBERS OF THE 20000223 STUDY GROUP

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(Indianapolis, IN), G. Sultany (Portland, OR), W. Surbeck (Tulsa, OK), J. Taborn (Kalamazoo, MI), P. Valen (La Crosse, WI), R. Valente (Lincoln, NE), D. Wallace (Los Angeles, CA), C. Weidmann (Van Nuys, CA).

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